REMARKS

This filing is presented in response to a final Office Action mailed December 4, 2008. A Request for Continued Examination (RCE) was previously filed on January 5, 2009. A one (1) month extension of time request and payment accompanies this filing. No additional fees are believed to be due.

In the Office Action mailed December 4, 2008, claims 43-49, 51, 120-127, and 129-135 were rejected under 35 USC §112, second paragraph for allegedly being indefinite.

Claims 1-8, 10, 43, 44, and 51 were rejected for allegedly being anticipated under 35 USC §102(b) by Hortin.

Claims 1, 6-8, 10, 43-49, 51, and 112-135 were rejected for allegedly being obvious based upon Hortin in view of Pittman et al.; Bakker et al.; and Ramabhadran.

In this amendment, claims 1, 112, and 113 have been amended. Claims 1-5, 8, 10, 43-49, 51, and 112-135 remain pending. Claims 6 and 7 were cancelled. And new claims 136-142 are presented for the Examiner's further consideration.

Applicant would like to thank the Examiner for the time and courtesy extended in the telephone interview conducted on February 19, 2009 between the Examiner and inventor Dr. Michael Kalafatis and Applicant's attorney. Although no agreement was reached, it was informative to discuss the Examiner's rejections and application of the cited art to the claims.

I. The Invention

The present discovery relates to the prevention and treatment of blood coagulation disorders. The invention finds particular application in conjunction with thrombin inhibitors.

Blood coagulation is a process whereby blood thickens and gradually becomes a clot. The process is vitally important to the stoppage of bleeding when blood vessels are damaged. Blood coagulation occurs through a complex series of molecular reactions, ultimately resulting in conversion of soluble fibrinogen molecules, present in the blood, into insoluble threads of fibrin. The result is a blood clot which consists of a plug of platelets enmeshed in the insoluble fibrin network.

Human disorders, called "thromboses," exist in which blood clots when it normally should not. Thrombosis is a major cause of death due to occlusion of arteries, which leads to heart attacks, strokes and peripheral ischemia (i.e., local deficiencies in blood supply). Thrombosis can also cause occlusion of venous blood vessels and result in pulmonary emboli.

In order to prevent or treat such thrombotic disorders, therapeutic methods to inhibit clot formation or to dissolve clots have been developed. Existing anticoagulants (that inhibit blood clot formation), for example, include heparin, which greatly increases activity of the physiologic anticoagulant, ATIII, in the blood. Warfarins are anticoagulants that are vitamin K antagonists. Since vitamin K is required for synthesis or functioning of a number of clotting factors (i.e., factors II, VII, IX and X, as well as a-thrombin and proteins C and S), sequestration of vitamin K inhibits coagulation.

The existing blood anticoagulants, however, produce undesirable side effects. For example, heparin administration can cause bleeding and thrombocytopenia (i.e., decrease in platelets). A disadvantage of warfarins is that it takes several days for their maximum effect to be realized. As with heparin, bleeding can also be a complication. Warfarins are also teratogens and can cross the placenta, causing fetal abnormalities when administered to pregnant women.

Therefore, there are problematic side effects with existing anticoagulant and thrombolytic drugs. Thus, there exists a need for an improved anticoagulant agent and/or pharmaceutical composition that inhibits coagulation to a greater degree and at a faster rate as compared to currently known agents or compositions, and particular, without the noted unwanted side effects. And, related to this, there exists a need for improved therapeutic methods for treating blood coagulation disorders, e.g. thromboses, by the administration of such improved anticoagulants or pharmaceutical compositions.

The present invention is based, at least in part, upon a discovery of certain peptides consisting of four or five amino acid sequences, i.e. DYDY or DYDYQ, that can directly bind with thrombin and thus serve as blood anticoagulants. Direct binding of the peptides to thrombin is described throughout the present application, and particularly at page 33.[1] The DYDY or DYDYQ sequence serves as an anticoagulant by binding to thrombin and inhibiting the activation of factor V to factor Va by thrombin.

[1] All page numbers are with regard to the parent application WO 2005/034844 as published.

This breaks the positive feedback loop between thrombin and factor V and thus inhibits the propagation of thrombin that would otherwise occur.

In another aspect according to the present discovery, it has been discovered that sulfonation of certain amino acids of the peptides of interest results in even greater inhibitory effects.

Accordingly, the present discovery provides a peptide having an amino acid sequence DYDY (SEQ ID NO. 10) or DYDYQ (SEQ ID NO. 11), and also includes peptides in which at least one of the Y amino acids is sulfonated, e.g. DY(-SO_3)DY (SEQ ID NO. 12), DYDY(-SO_3) (SEQ ID NO. 13), DY(-SO_3)DY(-SO_3) (SEQ ID NO. 14), DY(-SO_3)DYQ (SEQ ID NO. 7), DYDY(-SO_3)Q (SEQ ID NO. 8), DY(-SO_3)DY(-SO_3)Q (SEQ ID NO. 9), or combinations of these sequences. In accordance with the present discovery, these peptides have been found to significantly inhibit the generation of thrombin and thus, serve as anticoagulants.

II. Rejection of Claims 43-49, 51, 120-127, and 129-135 Under §112, Second Paragraph Must be Withdrawn

A. Terminology "Adapted for Inhibiting Thrombin Formation" is Acceptable

The Office rejected these claims[2] for use of the terminology "adapted for inhibiting thrombin formation." Specifically, the Office asserted that clarification was

[2] Actually, only claims 43, 120, and 128 were directly rejected under §112. However, since claims 44-49 and 51 depend (or ultimately depend) from claim 43, these claims were also rejected on the grounds noted for claim 43. Similarly, since claims 121-127 and 129-135 depend (or ultimately depend) from claims 120 and 128, these claims were also rejected on the grounds noted for claims 120 and 128.

required since "it is not clear what physical properties of the composition render it particularly adapted for this function."

It is respectfully requested that the Office identify a requirement that patent claims must identify specific physical properties of a composition that render the composition adapted for a particular function recited in the claim. Neither Applicant nor Applicant's attorneys are aware of any such requirement in the law. Instead, it is respectfully submitted that these claims are in fact sufficiently definite and meet the standard for §112, second paragraph because these claims would be understood by a person skilled in this field of art, and particularly, when read in view of the specification. This point was previously made in previously filed Amendment B, but no controlling authority or case precedent was provided by the Office in the most recent Action mailed December 4, 2008. The Office, again, is respectfully requested to identify these alleged requirements.

B. It is Not Necessary to Specify Source or Location of Thrombin

Regarding the Office's concern that the source or location of thrombin referenced in claims 43, 120, and 128 must be identified, this is also believed to not be necessary. Again, it is respectfully requested that the Office identify any requirement that patent claims directed to a composition for undertaking some function with regard to another agent, must recite the location or source of that agent. It is believed that limiting claims 43, 120 and 128 to thrombin at a specific location or from a specific source is not required. The prior art of record, it is respectfully submitted, does not require any of

these claims to be limited in this regard. The Office, again, is requested to identify these alleged requirements.

In summary, the term at issue, i.e. "adapted for inhibiting thrombin generation" refers to characteristics of the claimed composition which cause or otherwise result in thrombin generation to be inhibited. Thrombin, as known by those skilled in this field of art, is a coagulation protein existing in many biological systems, most notably humans. However, the claims at issue are not limited to inhibiting the generation of thrombin in humans or from humans. Again, it is submitted that the cited art does not require that the claims be limited as to a particular source or location of thrombin.

C. Mis-Reading of Claims

In response to Applicant's previous explanation concerning this matter, the Office asserted:

> Regarding this rejection, applicant alleges that the claims are definite (pages 12-13). These arguments have been fully considered, but they are not persuasive. The arguments appear to allege that the composition promotes the generation of thrombin when the composition comes in contact with a biological system that contains thrombin, but the claims are not so limited. It is noted that the only necessary component in each composition is a single peptide.

Page 3 of the December 4, 2008 Office Action.

It is respectfully noted that the Office's understanding of the present invention as recited in claims 43, 120, and 128 is incorrect. The claimed composition does not promote the generation of thrombin when the composition comes in contact with a biological system that contains thrombin. In contrast, and as previously explained herein, the claimed composition promotes the inhibition of thrombin generation.

D. Terminology "Adapted to" Commonly Used in Patent Claims

Furthermore, it is respectfully submitted that use of the phrase "adapted to" is commonly used in patent claims, and particularly in claims calling for chemical or medically-related subject matter. See for example claim 1 of US Patent 7,459,169; claim 5 of 7,491,496; claim 8 of 7,432,240; claim 4 of 7,485,771; claim 34 of 7,482,023; and claim 1 of 7,476,658. The present Examiner allowed claim 3 in US Patent 7,105,580 which contains the phrase "adapted to."

Upon further review, it is respectfully submitted that independent claims 43, 120, and 128 meet the requirement of definiteness under 35 USC §112, second paragraph. It is also submitted that dependent claims 44-49, 51, 121-127 and 129-135, also meet the requirements under §112. Accordingly, the present rejection under §112 should be withdrawn.

III. Rejection of Claims 1-8, 10, 43, 44, and 51 Under §102 by Horton Must be Withdrawn

The Office rejected claims 1-8, 10, 43, 44, and 51 under 35 USC § 102(b) for allegedly being anticipated, i.e. identically disclosed, by a previously cited 1990 article to Hortin.[3] As explained in greater detail herein, claims 6 and 7 have been cancelled. Thus, the claims at issue are claims 1-5, 8, 10, 43, 44, and 51.

[3] Hortin, G.L., "Sulfation of Tyrosine Residues in Coagulation Factor V," Blood, 1 September 1990, Vol. 76 No. 5, pages 946-952.

A. The Claimed Subject Matter

As described in the specification of the present application and in section I. herein, the present invention relates to a discovery of specific peptides, typically consisting of four or five amino acids, that have been found to significantly inhibit the generation of thrombin and thus serve as anticoagulants. These particular peptides include those containing the amino acid sequence DYDY, DYDYQ, and the sulfonated sequences of DYDY and DYDYQ, in which at least one of the Y amino acids is sulfonated.

Of the rejected claims 1-5, 8, 10, 43, 44, and 51; claims 1 and 43 are the only independent claims. Claims 1-5 recite a peptide having a sequence of amino acids which is identical to a sequence of consecutive amino acids found within amino acids 695 to 698 (SEQ ID NO. 10) of the human blood clotting factor Va.[4] Claim 8 is for a pharmaceutical composition comprising the peptide of claim 1. Claim 10 recites a peptide analogue that mimics the peptide of claim 1. Independent claim 43 recites a pharmaceutical composition adapted for inhibiting thrombin generation, the composition comprising a peptide that includes an amino acid sequence DYDY. Claim 44 recites the pharmaceutical composition of claim 43 further comprising a carrier. And, claim 51 recites a pharmaceutical composition that comprises a peptide analogue that mimics the peptide of the composition of claim 43.

[4] SEQ ID NO. 10 corresponds to the amino acid sequence DYDY.

B. Improper Reading of the Claims

In rejecting the claims at issue, the Office asserted that:

> The claims are interpreted as being drawn to a peptide comprising a sequence of amino acids that is identical to a sequence of at least 2 consecutive amino acids found within a 4-amino acid region of a longer reference sequence. In some dependent claims, the peptide has a particular activity or comprises a particular sequence. Some claims are drawn to compositions comprising the peptide or compounds that mimic the peptide in some way. It is noted for the record that claim 1 is currently so broad as to encompass any peptide that contains either the sequence DY or the sequence YD along with any other amino acids in any sequence. The scope of claim 43 encompasses any peptide that contains the sequence DYDY along with any other amino acids in any sequence.

Pages 3-4 of the Office Action.

It is respectfully submitted that an overly broad interpretation is being given to the term "peptide" in the claims at issue. Instead, the term "peptide" as used in the claims and by those skilled in the art, refers to a relatively short chain of amino acids, such as from about 2 to about 10 amino acids, and at most up to about 50 amino acids.

Apparently, under the overly broad interpretation of the term "peptide," the Office reads the claims as encompassing the disclosure by Hortin, and in particular, the mention of factor V by Hortin:

> Hortin teaches that the complete sequence of human coagulation factor V (hereafter "Factor V") was known at the time of the invention and that said sequence includes the sequence DYDYQ (page 946, column 1, paragraph 2; and Figure 6 at page 950, e.g.). Hortin teaches a solution comprising Factor V (page 946, column 2, last paragraph).

Page 4 of the Office Action.

The claims at issue do not encompass the disclosure of factor V by Hortin. Factor V as disclosed in the Hortin article is a protein, and includes about 2200 amino acids. Practitioners in the field of biochemistry refer to factor V as a protein and not as a peptide. Restated, factor V is not a peptide, and so is excluded by each of the claims

at issue, i.e., claims 1-5, 8, 10, 43, 44, and 51, since each of those claims expressly recites and thus, is limited to, a "peptide." Had Applicant intended to claim factor V or proteins, Applicant would have used the word "protein" in the claims and not expressly limited the claims to peptides.[5]

On pages 5-6 of the Office Action, the Office argued that the terms peptide and protein are synonymous with one another, and that the art makes no distinction between these terms. Applicant and Applicant's attorneys whole-heartedly disagree with such an assertion. However, Applicant's attorneys wish to refrain, at least at this time, from submitting evidence such as Declarations from experts in the field to demonstrate that peptides are not synonymous with proteins.[6]

C. Amendment to Independent Claim 1

In order to expedite allowance of the claims at issue, independent claim 1 has been amended to recite "a peptide consisting of an amino acid sequence DYDY...." In view of this amendment, a new independent claim 136 is presented for a "peptide consisting of an amino acid sequence DYDYQ...." New dependent claims 137-142 parallel dependent claims 2-5, 8, and 10 respectively. No new matter is added by any

[5] Applicant and Applicant's attorneys are also concerned with a statement in the previously quoted passage from the Examiner, "It is noted for the record that claim 1 is currently so broad as to encompass any peptide that contains either the sequence DY or the sequence YD along with any other amino acids in any sequence." No. Claim 1 recites in part, a peptide having a sequence of amino acids identical to a sequence of consecutive amino acids found within amino acids 695 to 698 (SEQ ID NO. 10) of the human blood clotting factor Va. As explained in the present application, this sequence of amino acids is DYDY. Thus, claim 1 recites, in part, a peptide having this identical sequence of consecutive amino acids, DYDY. Contrary to the Examiner's reading, claim 1 does not recite "any peptide that contains either the sequence DY or the sequence YD."

[6] Applicant's attorneys reserve this undertaking.

of these amendments or new claims as support is found throughout the present application, and particularly at p. 2-5, p. 11, and p. 14-17.

It is believed that claim 1 as now amended and containing the language "consisting of" is now readily distinguishable from Hortin. In support of this, it is noted that independent claims 112 and 116 also for peptides, include the language "consisting of" and those claims were not included in the present rejection under §102.

D. Proper Standard for Rejection

The legal standard for properly rejecting claims under §102 is as follows. "For a prior art reference to anticipate in terms of 35 USC §102, every element of the claimed invention must be identically shown in a single reference... These elements must be arranged as in the claim under review." In re Bond, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed." Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985).

Therefore, in order to properly reject any of claims 1-5, 8, 10, 43, 44, and 51, the Office must identify every element of each claim in the Hortin reference, and each element must be identically shown. That is, in order to properly reject a claim, Hortin must show exactly what is claimed.

E. Hortin Fails to Disclose Claimed Peptides

Independent claim 1 and claims 2-5 and 10 dependent therefrom, recite particular peptides. Claim 8 is for a pharmaceutical composition comprising the peptide

of claim 1. Independent claim 43 is for a pharmaceutical composition comprising a particular peptide. Claims 44 and 51 are also for pharmaceutical compositions according to claim 43.

In support of the rejection under §102, the Office argued that the claimed products and the prior art products are "identical," "substantially identical," or "the same":

> M.P.E.P. §2112 recites, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).
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> In this case, the claims encompass numerous peptides, including Factor V itself. Peptides cannot be separated from their inherent properties, and since the peptide as instantly claimed is identical in structure to the prior art peptide, the two necessarily have the same properties, including those recited in claims 2-5 and 43. Claims 10 and 51 are included in this rejection because a given composition is a perfect mimic of itself in every way.

Pages 4-5 of the Office Action.

Factor V is not a peptide. Furthermore, in no way is factor V disclosed by Hortin, identical to, substantially identical to, nor the same, as the peptides recited in claims 1-5, 8, 10, 43, 44, and 51. As previously explained, factor V is a protein and includes about 2200 amino acids. Claims 1-5 as now amended, specifically recite a "peptide consisting of an amino acid sequence DYDY...." More significantly, the claim language "consisting of an amino acid sequence DYDY" in independent claim 1, expressly excludes factor V disclosed by Hortin. Hortin fails to disclose a peptide consisting of an amino acid sequence DYDY. New claims 136-140 recite a "peptide consisting of an

amino acid sequence DYDYQ...." This claim language expressly excludes factor V disclosed by Hortin. For at least this reason, claim 1 and claims 2-5, 8, and 10 dependent therefrom, and new claims 136-140 are now readily distinguishable from Hortin.

Applicant does not dispute that factor V contains the sequence DYDY or DYDYQ. In fact, many other proteins contain this sequence of amino acids. However, as previously explained, the term "peptide" in the claims at issue excludes factor V and all other proteins that contain the noted sequences.

The article by Hortin, representing the state of the art from nearly twenty (20) years ago, also describes several fragments of factor V. One of the fragments is the well known factor Va. Hortin speculates a region of factor Va, using a predictive algorithm, as depicted in Figure 6.

However, Hortin entirely fails to disclose the peptide of independent claim 1. As noted, claim 1 recites a peptide consisting of an amino acid sequence DYDY which is identical to the sequence of consecutive amino acids 695 to 698 of factor Va. And new independent claim 136 recites a peptide consisting of an amino acid sequence DYDYQ which is identical to a sequence of consecutive amino acids found within amino acids 695 to 699 (SEQ ID NO. 11) of factor Va. Hortin discloses factor Va, and at best, only discloses a speculated region within the 105,000 dalton fragment Va of factor V. Hortin does not disclose a peptide consisting of the recited sequence of amino acids. Instead, Hortin discloses a complex molecule of about 2200 amino acids. Anticipation of a claimed peptide does not occur by merely pointing to various amino acids in a complex protein. Nor does anticipation of the peptides in the claims at issue occur by pointing to

amino acid sequence 695 to 698 or sequence 695 to 699 in factor Va speculatively shown by Hortin. Claim 1 does not recite nor include factor Va. Applicant is not claiming factor Va. Instead, claim 1 recites a peptide consisting of a specific amino acid sequence. Simply put, Hortin only discloses, and more accurately, only speculates as to the identity of a region of factor Va. Simply put, Hortin does not disclose a peptide containing the sequence of interest.

In the rejection of claims under §103 (which is addressed later herein), the Office combined the article to Hortin with several other references due to Hortin's admitted failure to disclose certain claimed features. In this regard, *the Office recognized that Hortin does not disclose the claimed peptides:* "Hortin does not exemplify a peptide in which one or both of the tyrosines in the DYDY or DYDYQ motif are sulfated. Hortin does not teach any fragments of factor V, e.g. the tetrapeptide DYDY or the pentapeptide DYDYQ." Page 10 of the Office Action. Thus, the Office recognized and admitted that Hortin fails to disclose the peptides DYDY and DYDYQ. For at least these reasons, the claims at issue are not anticipated by Hortin.

F. Hortin Fails to Disclose Claimed Pharmaceutical Compositions

Similarly, it will be appreciated that none of claims 8, 43, 44 or 51 is anticipated by Hortin. These claims all recite pharmaceutical compositions. Claim 8 recites a pharmaceutical composition comprising the peptide of claim 1. Independent claim 43 recites in part, a pharmaceutical composition including a peptide having an amino acid sequence DYDY. Claim 44 recites the composition of claim 43 further comprising a

carrier. And, claim 51 recites a composition comprising a peptide analogue that mimics the peptide of the composition of claim 43.

As previously explained, Hortin merely discloses factor Va and at best, speculates as to a region of amino acids within that factor. Hortin fails to disclose any type of pharmaceutical compositions having a peptide having the claimed sequence of interest, and entirely fails to disclose a pharmaceutical composition that includes a peptide analogue that mimics the claimed peptide.

In support of the claims for pharmaceutical compositions, the Office contended:

> Regarding the teaching of a pharmaceutical composition that comprises the peptides of the claims, Hortin teaches Factor Va in a physiological buffer containing HEPES and salt (page 946, column 2). The buffer of Hortin does not contain any components that would preclude its being administered to a patient. If the composition of claim 43 necessarily includes some particular component, the claim should reflect the same.

Page 6 of the Office Action.

Apparently, the Office asserts that a composition containing factor Va, HEPES and salt is identical, i.e. anticipates, pending claim 43. HEPES is a well known sulfonic acid based organic chemical buffering agent. It is well known that HEPES is an irritant and may be harmful if swallowed, inhaled or absorbed through the skin. It is unclear how the Office contends that HEPES corresponds to a pharmaceutical composition.

G. Hortin Fails to Disclose Peptide Analogue

Claim 10 recites a peptide analogue that mimics the peptide of claim 1. Also, previously discussed composition claim 51 recites a peptide analogue.

Hortin entirely fails to disclose any type of peptide analogue. The present rejection fails to identify any such disclosure in Hortin, and for this reason alone must be withdrawn.

H. Additional Reasons Why Claims 1-5, 8, and 10, Are Novel Over Hortin

Independent claim 1 as now amended, parallels previously filed and currently pending independent claim 112. Since claim 112 was not now nor ever rejected under §102 for anticipation by Hortin, it is respectfully submitted that claim 1 is now novel over Hortin. Apparently, the Examiner is of a view that if the length and sequence of the peptides are limited, then such claims would not be anticipated by Hortin. In this regard, the Examiner stated "[c]laim 112, for example, which limits the length and sequence of the peptide to the tetrapeptide DYDY, is not included in this [§102] rejection." Page 6 of the Action (bracketed text added).

On pages 6-8 of the Office Action, an extensive argument of anticipation by inherency was presented with regard to claims 2-5. That argument then concludes with an assertion that "the properties of claims 2-5 flow from the fact that the peptide instantly claimed is identical to that taught by Hortin." Page 8 of the Office Action. Again, there is no basis for a view that the claimed peptides are "identical" to factor Va or factor V disclosed by Hortin. Furthermore, claims 2-5 depend upon claim 1, and so contain all the recitations of that claim. Since claim 1 is now submitted to be allowable over Hortin, so too are claims 2-5.

I. Summary Concerning the Anticipation Rejection

It is respectfully submitted that upon further review, the Examiner will appreciate that the present rejection of claims 1-5, 8, 10, 43, 44, and 51 under §102 should be withdrawn. This is particularly so in view of the amendment presented to independent claim 1. Hortin does not disclose the claimed peptides, pharmaceutical compositions including such peptides, or the peptide analogues recited in the claims in dispute.

IV. Rejection of Claims 1, 6-8, 10, 43-49, 51 and 112-135 Under §103 by Hortin in View of Pittman et al.; Bakker et al.; and Ramabhadran Must be Withdrawn

A. Current State of the Law

In support of the present rejection under §103, the Examiner cited the recent Supreme Court decision, KSR International Co. v. Teleflex Inc., 550 U.S. 398, 82 USPQ2d 1385 (US 2007). Before turning attention to this ground of rejection and the Examiner's application of KSR, it is instructive to review the impact of KSR and several decisions by the Court of Appeals for the Federal Circuit applying KSR.

1. The Impact of KSR

The Supreme Court in KSR affirmed the analysis and factors previously set forth in its earlier decision, Graham v. John Deere Co., 383 US 1, 148 USPQ 459 (1966). As explained in greater detail herein, the Supreme Court did not overturn the Federal Circuit's "teaching-suggestion-motivation" (TSM) test for determining whether an

invention is obvious.[7] Rather, the Court disapproved of the manner in which the Federal Circuit previously applied the test. The Court stated in this regard that the TSM test represented "a helpful insight" and further, that "[t]here is no necessary inconsistency between the idea underlying the TSM test and the Graham analysis."[8]

In a memorandum to its examiners issued days after KSR was handed down, the U.S. Patent and Trademark Office emphasized that "[t]he Court did not totally reject the use of teaching, suggestion, or motivation to combine the prior art as a factor in the obviousness analysis."[9] The memorandum concluded: "Therefore in formulating a rejection under 35 U.S.C. §103a based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed."

2. Post-KSR Decisions

In Takeda Chemical Industries, Ltd. v. Alphapharm Pty, Ltd, 492 F.3d 1350 (Fed. Cir. 2007), decided after KSR, the Federal Circuit denied Alphapharm's assertion that the KSR decision required a holding that certain claims were obvious. In Takeda, claims for an antidiabetic compound had been previously upheld by a lower court.

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[7] To counter the use of hindsight by an examiner when determining the obviousness of an invention, the Federal Circuit (and its predecessor, the Court of Customs and Patent Appeals) developed and refined a test, i.e. the TSM test, that requires that the examiner provide an objective reason why a person skilled in the art would combine the prior art references. The objective reason should come from "the knowledge of one of ordinary skill in the art" of the invention, or perhaps from "the nature of the problem to be solved" by the invention.

[8] KSR, 550 U.S. at ____, 82 USPQ2d at ____.

[9] Memorandum from Margaret A. Focarino, Deputy Commissioner for Patent Operations, to Technology Center Directors (May 3, 2007).

Alphapharm appealed that decision to the Federal Circuit on grounds that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound.[10] And thus, under Alphapharm's argument, the claims were obvious, and particularly in view of the recent KSR decision.

In upholding the claims at issue, the Federal Circuit noted that one of the prior art references taught compound b "exhibited negative properties that would have directed one of ordinary skill in the art away from that compound." Thus, the court recognized that a prior art "teaching away" is significant and can support the nonobviousness of patent claims.

The court continued and explained its decision upholding the nonobviousness of the claimed compound in view of the recent KSR decision:

> The KSR Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." KSR, 127 S. Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under §103." Id. That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try."

Takeda, 492 F.3d at ___.

More recently, in another post-KSR decision, the Federal Circuit again upheld the TSM test and noted that such test, flexibly applied, is necessary to avoid hindsight

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[10] By "lead compound," Alphapharm referred to a compound in the prior art that would be most promising to modify in order to improve upon its antidiabetic activity and obtain a compound with better activity, i.e. the patented compound. Upon selecting that compound for antidiabetic research, Alphapharm asserted that one of ordinary skill in the art would have made two obvious chemical changes. Thus, Alphapharm's obviousness argument depended on a preliminary finding that one of ordinary skill in the art would have selected compound b as a lead compound.

analysis, Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358 (Fed. Cir. 2008):

> As this court has explained, however, a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis such as occurred in this case. In re Translogic Tech., Inc., 504 F.3d 1249, 1257 (Fed. Cir. 2007) ("[A]s the Supreme Court suggests, a flexible approach to the TSM test prevents hindsight and focuses on evidence before the time of invention."). The TSM test, flexibly applied, merely assured that the obviousness test proceeds on the basis of evidence – teachings, suggestions (a tellingly broad term), or motivations (an equally broad term) – that arise before the time of invention as the statute requires.

Ortho-McNeil, 520 F.3d at ___.

Therefore, the current state of the law may be summarized as follows. The Graham factors still control an obviousness inquiry. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. KSR, 127 S. Ct. at 1734 (quoting Graham, 383 U.S. at 17-18).

The TSM test is also alive and well, albeit more flexible in its application.

Whether a reference teaches away is also still a critical factor in reaching an obviousness determination.

And, in reaching an obviousness determination based upon a combination of prior art elements, it remains absolutely necessary to identify objective reasons, i.e. evidence, why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

B. Proper Application of the Law to the Claims at Issue

The Office rejected claims 1, 6-8, 10, 43-49, 51, and 112-135 under 35 USC §103(a) for allegedly being obvious based upon the article to Hortin, in view of articles to Pittman et al., Bakker et al., and Ramabhadran.[11]

In order to assess whether the subject matter of each of these claims is obvious, it is first necessary to apply the four factors from Graham.

1. Scope and Content of the Prior Art

Hortin was previously described in section III. herein.

Pittman et al.,[12] representing the state of the art from fifteen (15) years ago, note that factor V is a cofactor in the blood coagulation cascade. Pittman et al. note that factor V requires activation by thrombin for functional activity. Pittman et al. continue and describe sulfation of factor V and that such sulfation affects the rate of activation by thrombin: "[S]ulfation of factor V is required for rapid cleavage by thrombin" p. 6956.

The Examiner contended that:

> Pittman teaches that inhibiting sulfation of Factor V inhibits its procoagulant activity (page 6955, column 1, under "Sulfation is required..."). Specifically, Pittman teaches that Factor V must be sulfated to undergo binding and subsequent cleavage by thrombin (page 6956, column 1; and Figure 3B). Pittman concurs with Hortin that tyrosines 696 and 698 are likely candidates for the sulfation (page 6957, column 1, under "Discussion"). Pittman also teaches methods for sulfating proteins (pages 6953 and 6954).

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[11] On page 9 of the Office action, the action stated "[t]his application currently names joint inventors..." It is believed that inclusion of this statement in the Office action is a typographical error. The present application names a single inventor, Michael Kalafatis.

[12] Pittman, D.D., et al., "Posttranslational sulfation of factor V is required for efficient thrombin cleavage and activation and for full procoagulant activity," Biochemistry, Vol. 33, No. 22, pp. 6952-6959, 1994.

Page 10 of the Office Action.

A fair and objective reading of Pittman requires recognition of other teachings by Pittman. Pittman also state that tyrosines 696 and 698 (cited by the Examiner), in addition to those at positions 1494, 1510, 1515 and 1565, are mere speculated guesses as to sites in factor V for sulfonation. Pittman clearly admit in this regard that, "the precise sites of tyrosine sulfation in factor V remain to be elucidated..." p. 6957. In discussing potential mechanisms as to how sulfonation of factor V affects procoagulant activity, Pittman also admit that, "we do not know if efficient thrombin cleavage of the light chain [fragment of factor V] also requires tyrosine sulfation." p. 6957 (bracketed text added).

The focus of the cited study by Pittman was to investigate the effects of sulfation of factor V upon the kinetics of (i) cleavage and activation of that factor by thrombin and (ii) the intrinsic activity of factor Va. Pittman demonstrated the importance of sulfation for factor V activity by administering sodium chlorate, which is a known inhibitor of sulfation. Increasing concentrations of sodium chlorate inhibited the extent of sulfation of factor V. Pittman concluded that "sulfation of factor V is required for efficient thrombin activation."

Bakker et al.,[13] also from fifteen (15) years ago, describe functional properties of factor Va, by investigating a modified form of this factor lacking a certain range of amino acids. An enzyme from certain snake venom was identified as converting factor Va into a molecule having greatly reduced cofactor activity. The authors concluded that the loss

[13] Bakker HM et al. 1994. Functional properties of human factor Va lacking the Asp683-Arg709 domain of the heavy chain. J Biol Chem 269: 20662-20667.

of a 27-amino acid peptide from factor Va impaired interaction between the treated factor Va with prothrombin and a cofactor.

The Examiner asserted that:

> Bakker teaches that the portion of Factor V heavy chain required to bind thrombin is the C-terminal 27 amino acids thereof, which comprises the DYDYQ motif (see Table II at page 20665 and page 20664, column 1, first full paragraph). Bakker further teaches that these 27 amino acids are responsible for the binding of Factor V to prothrombin (page 20667, column 1, first full paragraph).

Page 10 of the Office Action.

No. Contrary to the Examiner's assertion, Bakker does not teach "that the portion of Factor V heavy chain required to bind thrombin is the C-terminal 27 amino acids thereof." Bakker is concerned with the mechanism of how the snake venom enzyme reduces activity of factor Va. Bakker compared rates of prothrombin activation by factor Va and the treated factor Va. Bakker entirely fails to provide any teaching or even suggestion as to binding thrombin, or more particularly how or what region(s) of factor V or fragments thereof, may be responsible for binding to thrombin.

Thrombin is not the same as prothrombin. Thrombin is produced by an enzymatic cleavage of two sites on prothrombin by activated factor X. Prothrombin is produced in the liver. Although thrombin is derived from prothrombin, these agents are different from one another and have entirely distinguishable roles and functions in the blood coagulation process.

Perhaps of greatest significance is the fact that Bakker teaches away from the present invention. This is explained in detail herein in section IV. C.

Ramabhadran,[14] also from about fifteen (15) years ago, describes that peptides can be chemically synthesized.

2. Differences Between the Prior Art and the Claims

a. Failure to Teach the Claimed Peptides

None of the cited art, i.e. the articles to Hortin, Pittman, Bakker, and/or Ramabhadran, taken in any combination, teach or even suggest the particular peptides recited in the claims at issue. As previously explained in section III. herein, none of these peptides are disclosed by Hortin. Instead, Hortin describes the protein factor V.

The Examiner in the most recent Office Action, admitted that Hortin does not teach the claimed peptides:

> Hortin does not exemplify a peptide in which one or both of the tyrosines in the DYDY or DYDYQ motif are sulfated. **Hortin does not teach** any fragments of Factor V, e.g. **the tetrapeptide DYDY or the pentapeptide DYDYQ.**

Page 10 of the Office Action (emphasis added).

Pittman also fails to teach the claimed peptides. Pittman merely describes several fragments of factor V.

At most, Bakker describes incubation of factor Va with a certain protease from snake venom which cleaved a 27 amino acid fragment. Bakker's teaching is described in greater detail herein. However, with regard to the specific peptides at issue, Bakker entirely fails to teach those specific peptides.

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[14] Ramabhadran TV. 1994. Pharmaceutical Design and Development: A Molecular Biology Approach. Ellis Horwood, Hertfordshire UK. Pages 40, 42, and 43.

Ramabhadran in many respects, is not even relevant to the present rejection. Ramabhadran entirely fails to teach the specific peptides recited in the claims at issue.

Thus, none of the cited art teach or describe the specific peptides called for in the claims at issue.

b. Failure to Teach Direct Binding Between the Claimed Peptides and Thrombin

Another fatal flaw in the present obviousness rejection is that the Office assumes or rather speculates that one or more of the prior art references teaches binding between thrombin and factor V, and particularly that such binding occurs at the amino acid sequences of interest. Specifically, in support of the present rejection, the Office asserted:

> Pittman teaches that Factor V must be sulfated to undergo binding and subsequent cleavage by thrombin

Page 10 of the Action.

> Bakker teaches that the portion of Factor V heavy chain required to bind thrombin is the C-terminal 27 amino acids thereof...

Page 10 of the Action.

> [B]ecause Hortin teaches that Factor V is bound and cleaved by thrombin...

Page 12 of the Action.

No. There is absolutely no evidence presented in any of the noted references for direct binding between factor V and thrombin. And, more significantly, none of the cited references teach or describe binding between the claimed peptides and thrombin.

None of Pittman, Bakker, and particularly Hortin present any evidence such as data demonstrating such alleged binding. And, furthermore, none of Pittman, Bakker, nor Hortin show that DYDY, DYDYQ, or the sulfonated versions of these sequences are direct binding sites for thrombin.

As explained in section I. herein, a significant feature of the present invention is the discovery of specific amino acid sequences, i.e. DYDY or DYDYQ, that directly bind with thrombin and thus serve as anticoagulants. The present invention provides peptides that consist of these amino acid sequences and which then upon binding to thrombin, inhibit the activation of factor V to thereby inhibit subsequent thrombin generation.

Independent claim 112 and new independent claim 136 both expressly recite in part, that the peptide is "for direct binding to thrombin." Claim 112 was amended to recite this significant aspect of the present invention. No new matter is added by the amendment to claim 112 or by this recitation in claim 136, as support is found throughout the present application and particularly on page 33.

3. Level of Ordinary Skill in the Pertinent Art

The Supreme Court in KSR also recognized that an invention may not be obvious if its implementation was beyond the level of ordinary skill in the art. If however, the invention is the result of "ordinary innovation" it is then "not the subject of exclusive rights under the patent laws." Specifically, the Supreme Court in KSR explained in this regard:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

KSR, 550 U.S. at ____.

The patent at issue in KSR was directed to an adjustable gas pedal system for a car. Those types of inventions involving mechanical assemblies frequently result from a finite number of identified, predictable solutions.

In contrast, biotechnology is an inherently unpredictable art. In the biotechnology fields, and specifically in the context of the present invention, often there are simply too many possible avenues to pursue in order to render the claimed solution obvious and one of ordinary innovation. Furthermore, the possible or potential solutions are not predictable. No doubt the Examiner will appreciate that there exists a high degree of unpredictability in how different elements, agents and chemical species, interact and in the results they achieve. This is particularly pronounced in complex biological systems.

Contrary to the Office's convenient, conclusory allegations of obviousness, the prior art, i.e. articles to Hortin, Pittman, Bakker, and Ramabhadran, teach an extremely large number of sequences of amino acids. Factor V includes approximately 2200 amino acids. None of these references provide any guidance as to which amino acids should be chosen for further investigation, or what further investigations may be desirable. Pittman admit that the sites of tyrosine sulfation in factor V remain to be identified. In fact, Pittman further admit that it is unknown whether efficient thrombin cleavage requires tyrosine sulfation. Nor do any of these references teach or even

suggest a strategy for inhibiting thrombin generation by identifying particular amino acid sequences for directly binding to thrombin. Bakker teaches binding to prothrombin.

This field of art is extremely unpredictable and a skilled artisan, contrary to the Examiner's arguments, would not have had a reasonable expectation of success in identifying the claimed sequences of amino acids, and/or identifying the claimed peptides, from the numerous possibilities presented. Nor would a skilled artisan have had a reasonable expectation of success in identifying the particular sequences which can be utilized in the claimed peptides for direct binding to thrombin, thereby serving as important anticoagulant agents.

4. Objective Evidence of Nonobviousness

The present application contains evidence of the nonobviousness of the present invention. Figure 9B reveals that DYDY is a potent inhibitor of factor V because this peptide impairs cleavage of the factor which is a required step during sequential activation of that factor.

Figure 10A demonstrates the improved inhibition resulting from the sulfonated peptides of interest as compared to non-sulfonated peptides.

Figure 10B illustrates the surprising and unexpected effects of increasing concentration of the peptide DYDYQ upon the reaction kinetics of blood coagulation.

Similarly, Figure 11A illustrates inhibition by the double sulfonated peptide DYDYQ. Such dramatic reductions are remarkable.

Figure 11B illustrates the surprising and unexpected effect of increasing concentration of the sulfonated peptide DYDYQ.

Figure 12 illustrates clotting time as a function of various peptides according to the present invention.

And Figure 13 illustrates clotting time by various claimed peptides.

This evidence and other data and information presented in the present application is objective evidence of nonobviousness, and thus must be considered in support of the patentability of the claims at issue.

On page 13 of the Office Action, the Examiner contended that:

> Figures 10-13 have been considered, but it is submitted that these figures only provide information about a few embodiments within the broader claims. Furthermore, applicant's reply does not clearly indicate what aspects of this data are unexpected; rather, the reply refers to the figures generally.

The Examiner's arguments are not understood. The data presented in these figures is explained in detail in the present application and particularly on pages 46-49. The figures provide extensive information not only about "a few embodiments within the broader claims" but for all of the claimed peptides. The Examiner is respectfully requested to review this evidence in greater detail.

In support of ignoring these figures, the Office cited §716.02(b) of the MPEP, see p. 14 of the Office Action. That section of the MPEP is directed to which party bears the initial burden of evidence of nonobviousness. Applicant's attorneys do not dispute that this initial burden is on Applicant. The noted evidence was previously presented. The relevance and significance of that evidence was previously explained, and is again summarized herein. It is respectfully submitted that Applicant has satisfied its burden in accordance with the cited section of the MPEP.

It is respectfully submitted that the Examiner will appreciate that prior to the present invention, a longstanding need existed in the prior art for an improved strategy

for addressing blood coagulation disorders, and specifically, thrombotic disorders. Currently known blood anticoagulants produce undesirable side effects. Thus, improved agents, pharmaceuticals, and treatment methods are needed. These facts are described in the background section of the present application.

5. Analysis

Therefore, in applying the Graham factors, it is to be appreciated that the cited art fails to teach or describe any of the claimed peptides. It was admitted by the Office that Hortin does not teach the tetrapeptide DYDY or the pentapeptide DYDYQ. None of the other cited art, i.e. Pittman, Bakker, and/or Ramabhadran, remedy the deficiencies of Hortin and teach or describe these specific peptides. Furthermore, the cited art also fails to teach or describe direct binding of the claimed peptides with thrombin. None of Pittman, Bakker, Ramabhadran and particularly Hortin present any evidence of this. The nonobviousness of the claims at issue is further indicated by considering the inherently unpredictable field in which the present invention was discovered. The present invention was not reached by identifying a finite number of predictable solutions and then pursuing the known solutions to thereby arrive at the presently claimed subject matter.

Analyzing the grounds of the present rejection in detail further reveals inconsistencies, various weaknesses, deficiencies, and misinterpretations of prior art. In support of the present rejection, the Office asserted:

> A person of ordinary skill in the art would have had a reasonable expectation of success in sulfating either or both of the tyrosine residues at positions 696 and 698 within Factor V because Hortin and Pittman both teach that these residues are within consensus sequences for sulfation. The skilled artisan would have been

> motivated to sulfate one or both of these residues in Factor V because Pittman teaches that Factor V is not active unless it is sulfated.

Pages 10-11 of the Office Action.

This is a prime example of hindsight reconstruction of the pending claims, reached by benefit of the present invention itself! No explanation was provided as to how within the 2200 amino acid sequence of factor V, the tyrosines at positions 696 and/or 698 were arrived at. Hortin in point of fact, does not adequately teach that these sequences are for sulfation. As explained in greater detail herein, Hortin states that these locations are merely possible sites, and that the precise sites remain to be established. Moreover, Hortin entirely fails to provide any teaching as to the function of the speculated sites, and particularly their function in a blood coagulation process. Pittman, as previously explained, teaches that the "sites of tyrosine sulfation in factor V remain to be elucidated." Moreover, it is inaccurate to state that "Pittman teaches that Factor V is not active unless it is sulfated." No. Pittman only concluded in this regard that the extent of sulfation of factor V affects the efficiency of thrombin activation.

The Office continued and asserted:

> The person of ordinary skill in the art would have had a further reasonable expectation of success in producing short peptides including tyrosine residues 696 and 698 because Hortin teaches that the entire sequence of Factor V was known at the time of the invention and because Ramabhadran teaches that peptides of up to 50 amino acids in length and with a given sequence may be chemically synthesized.

Page 11 of the Office Action.

The Office assumes that the claimed peptides including tyrosine residues 696 and 698 could be produced because the entire sequence of factor V was known, and chemical synthesis techniques are known for producing peptides of up to 50 amino acids in length with a given sequence. Applicant does not dispute that techniques are

known for producing peptides of up to 50 amino acids in length with a given sequence. Nor does Applicant dispute that the sequence of factor V was known at the time of the present invention. So too are the sequences of many other proteins and factors. So what? Again, the present invention is based, at least in part, upon a discovery of certain peptides consisting of four or five amino acid sequences, i.e. DYDY or DYDYQ, that can directly bind with thrombin and thus serve as blood anticoagulants. The DYDY or DYDYQ sequence serves as an anticoagulant by binding to thrombin and inhibiting the activation of factor V to factor Va by thrombin. None of the cited art teach or describe this.

The Office continued and asserted:

> The skilled artisan would have been motivated to produce such peptides because Bakker teaches that the C-terminal portion of Factor V heavy chain, which comprises tyrosine residues 696 and 698, is the domain required to bind prothrombin;

Page 11 of the Office Action.

This statement is inconsistent with a previous statement by the Office on page 10 of the Office Action that "Bakker teaches that the portion of Factor V heavy chain required to bind thrombin is the C-terminal 27 amino acids thereof..." Which agent does the Office consider the portion of factor V heavy chain binding with? Thrombin or prothrombin? As previously explained herein, Bakker compared rates of prothrombin activation by factor Va and a modified form of factor Va resulting from exposure to snake venom. Furthermore, as explained herein, Bakker actually teaches away from the present invention.

The Office continued and contended:

> the skilled artisan would have been motivated to determine which of these 27 residues is necessary for the interaction and which are not.

Page 11 of the Office Action.

No explanation or basis was provided by the Office for this belief. That is, no reasons in the form of objective evidence were provided by the Office as to why or how a skilled artisan would have been motivated to determine which of these 27 residues is necessary for the interaction and which are not. To what "interaction" does the Office refer? Again, no specific analysis was provided in this regard.

The Office continued and asserted:

> Furthermore, sulfating these residues would have constituted routine experimentation on the part of the skilled artisan, since Pittman teaches methods for doing so. The skilled artisan would have been motivated to sulfate the tyrosine residues because Pittman and Horton both teach that they may be sulfated *in vivo*, because Bakker teaches that these residues are within a domain that binds prothrombin, and because Pittman teaches that Factor V must be sulfated to bind thrombin. Therefore, the skilled artisan would have endeavored to learn whether the tyrosine residues in the 27-amino acid peptide of Bakker need be sulfated to bind prothrombin. In light of the practical teachings and predictions of the art, the selection of the peptide sequence and sulfation pattern would have constituted routine experimentation at the time of the invention. See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Pages 11-12 of the Office Action.

The contention that "sulfating these residues [i.e. the 27 amino acid fragment described by Bakker] would have constituted routine experimentation on the part of the skilled artisan since Pittman teaches methods for doing so is a convenient and impermissible leap to a conclusion of obviousness. First, upon what objective teachings in the cited art is this belief based? How would a skilled artisan, seeking to identify specific peptides for direct binding to thrombin, have arrived at the Bakker reference and its description of snake venom cleaving off a sequence of 27 amino acids? Furthermore, it does not follow that sulfating "these residues" would be obvious because Pittman teaches methods for doing so. Pittman was concerned with the

effects of sulfation of factor V upon kinetics of (i) cleavage and activation of factor V and (ii) the intrinsic activity of factor Va. The Office can not ignore other significant teaches by Pittman that the "sites of tyrosine sulfation in factor V remain to be elucidated" and "we do not know if efficient thrombin cleavage of the light chain [fragment of factor V] also requires tyrosine sulfation."

Hortin merely speculates as to "probable sites of sulfation" in the 2,196 amino acids of factor V. Hortin estimates that "the amino acid sequence of factor V contains six tyrosines that are likely sites of sulfation: residues 696, 698, 1494, 1510, 1515, and 1565." p. 950. However, in this regard Hortin also state that "[t]he precise sites of sulfation in factor V remain to be established." p. 950.

Conveniently picking and choosing among various speculations in the cited references, while ignoring other statements in the same references as to doubts associated with the speculations is yet another instance of impermissible hindsight reconstruction of the pending claims that can only be reached by benefit of the present invention.

The Office continued and asserted:

> The skilled artisan would have had a reasonable expectation that peptides made as suggested by the art as set forth above would inhibit thrombin activity because Hortin teaches that Factor V is bound and cleaved by thrombin, Bakker teaches that the C-terminal 27 amino acids of Factor V are the portion involved in binding thrombin, and Pittman and Horton teach that residues 696 and 698 are likely required for thrombin binding. See *KSR*.

Page 12 of the Office Action.

No. This conclusion simply does not follow from the collection of Hortin, Pittman, and Bakker. Hortin does not teach in any manner that any peptides would inhibit thrombin activity. The Office is respectfully requested to identify the specific statements

by Hortin that purportedly teach this. Hortin, at most, speculates that six tyrosines at amino acid locations 696, 698, 1494, 1510, 1515, and 1565 are likely sites of sulfation. The Office fails to explain why amino acid locations 696 and 698 are to be selected and why locations 1494, 1510, 1515, and 1565 are all to be ignored. Further, the Office fails to provide any objective reasons, i.e. evidence, as to the significance of these sites. Even if their teaching as sulfation sites may be fairly inferred from the art (which Applicant contests due to the fact that the cited references clearly note that the various locations are merely speculated and that the locations remain to be identified), the cited art still fails to teach the specific peptides consisting of the four or five recited amino acids.

The Office continued and argued:

> It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to produce peptides using the method of Ramabhadran that correspond to various portions of the 27 amino acids of Factor V taught by Bakker to be involved in binding thrombin in order to determine which portions of this fragment are necessary for thrombin binding. It would have been further obvious to sulfate one or more of the tyrosine residues within the resulting peptide because Pittman teaches that sulfation is required for activity and teaches methods for sulfating proteins.
>
> Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Page 12 of the Office Action.

As previously explained, Bakker does not provide any teaching as to binding thrombin, or more particularly, how or what region(s) of factor V or fragments thereof may be responsible for binding to thrombin. Instead, Bakker is concerned with rates of prothrombin activation by Factor Va and a modified form of that factor resulting from exposure to snake venom. The present rejection is based upon a misinterpretation of the teachings of Bakker. Pittman, as previously explained, notes that the sites of

tyrosine sulfation in factor V remain to be elucidated. Hortin merely speculates as to several possible sites for sulfation in factor V. Hortin explains that the precise sites remain to be identified. Hortin entirely fails to provide any guidance as to the function of the speculated sites, and particularly, the function of those sites in a blood coagulation process.

A *prima facie* case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. "If the examiner fails to establish a *prima facie* case, the rejection is improper and will be overturned." In re Rijckaert, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). A *prima facie* case has not been established, and thus, the present rejection is improper and must be withdrawn.

C. Bakker Teaches Away

Moreover, it is significant that one of the references relied upon for the present rejection actually teaches away from the subject matter of the pending claims. Bakker et al. describe a modified factor Va designated as Va_{NO} that is obtained by incubating factor Va with an enzyme from the venom of *N. naja oxiana*. Bakker et al. describe several comparative tests in which the inhibitory modified factor Va is compared to untreated factor Va:

> With the factor Xa-Va complex the reaction was characterized by a Km for prothrombin of 0.24μM and a V_{max} of 6860 mol of prothrombin activated per min. per mol of factor Xa....In the case of the factor Xa-Va_{NO} complex the Km was less favorable (0.83 μM), whereas V_{max} was slightly higher (7685 mol of prothrombin activated per min. per mol of factor Xa).

P. 20665 of the article to Bakker et al. In addition, see Fig. 5 on p. 20666.

A person skilled in this field of art, desirous of identifying a strategy or agent for inhibiting thrombin generation, after considering the article to Bakker et al. **would be motivated to investigate other amino acid regions in factor Va besides those of the 27 amino acid section that were cleaved from the factor by the snake enzyme.** This is because the modified factor Va_{NO} causes greater prothrombin activation as evidenced by a higher Km and faster V_{max} than unmodified factor Va. Thus, this is why Bakker et al. conclude that, "[t]hus, the final 27 carboxyl-terminal residues of the factor Va...do not play a role in the increase of the k_{cat} of prothrombin activation." p. 20667.

No doubt the Office will appreciate that such a teaching away effectively rebuts the present rejection. "A prima facie case of obviousness can be rebutted if the applicant...can show 'that the art in any material respect taught away' from the claimed invention." In re Haruna, 249 F.3d 1327, 58 USPQ2d 1517 (Fed. Cir. 2001). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." Tec Air, Inc. v. Denso Manufacturing Michigan Inc., 192 F.3d 1353, 52 USPQ2d 1294 (Fed. Cir. 1999).

More recently, the Federal Circuit expressly upheld the significance of a reference teaching away, in Takeda. That is exactly the situation here with Bakker.

The Office disputed this previously presented analysis of Bakker and how Bakker teaches away. In this regard, the Office contended:

> It is respectfully submitted that applicant has misinterpreted the teachings of Bakker. The Va_{NO} of Bakker that is discussed in the passage referenced by applicant (page 20665 of Bakker and page 24 of the reply) is not a peptide that consists of the

> last 27 amino acids of Factor Va, but rather a peptide that includes the entire sequence of Factor Va except for these last 27 amino acids. "[T]he heavy chain of factor Va_{NO} had a slightly increased electrophoretic mobility, indicating the loss of a small peptide ... from the heavy chain" (page 20663, column 2, third full paragraph). Bakker teaches that when the C-terminal 27 amino acids are removed from Factor Va, the resulting peptide (Va_{NO}) activates thrombin more effectively than does native Factor Va; the reply appears to stipulate to the fact that Va_{NO} is a less effective thrombin inhibitor than is Factor Va. The skilled artisan would have concluded from these teachings that these C-terminal 27 amino acids possess an activity that inhibits thrombin activation. This C-terminal portion would therefore have been a region of interest to artisans seeking thrombin inhibitors.

Page 14 of the Office Action.

Applicant never asserted that Bakker describes comparative testing involving "a peptide that consists of the last 27 amino acids of Factor Va" as stated above. No. Instead, Applicant previously explained and continues to urge that Bakker teaches that a modified factor Va_{NO} causes greater prothrombin activation as evidenced by a higher Km and faster V_{max} than unmodified factor Va. It is for this reason that an artisan, interested in inhibiting thrombin generation, would be motivated to investigate other amino acid regions in factor Va besides those of the 27 amino acid section that were cleaved from the factor by the snake enzyme. It is indisputable that Bakker conclude that "[t]hus, the final 27 carboxyl-terminal residues of the factor Va...do not play a role in the increase of the K_{cat} of prothrombin activation."

Therefore, the present rejection has been effectively rebutted and for at least this reason, must be withdrawn.

D. Rejection Based on Hindsight Reconstruction

In support of the present obviousness rejection, the Examiner asserted:

> Pittman teaches that inhibiting sulfation of Factor V inhibits its procoagulant activity (page 6955, column 1, under "Sulfation is required..."). Specifically, Pittman teaches that Factor V must be sulfated to undergo binding and subsequent cleavage by thrombin (page 6956, column 1; and Figure 3B). Pittman concurs with Hortin that

> tyrosines 696 and 698 are likely candidates for the sulfation (page 6957, column 1, under "Discussion"). Pittman also teaches methods for sulfating proteins (pages 6953 and 6954).

Page 10 of the Office Action.

The Office argues in the above quoted passage that Hortin and Pittman teach that residues 696 and 698 are likely required for thrombin binding and that "these residues are within consensus sequences for sulfation." Pages 10-11 of the Office Action. The Office then, without identifying any basis in the art, concludes that it would have been obvious to provide a peptide for inhibiting thrombin generation having a sequence of amino acids DYDY (claims 1, 112) or a sequence of amino acids DYDYQ (claim 116); or a pharmaceutical composition for inhibiting thrombin generation including a peptide having the sequence of amino acids DYDY (claims 43, 120) or a sequence of amino acids DYDYQ (claim 128).

As previously noted, the Office admitted that Hortin does not teach either of the peptides DYDY or DYDYQ. Page 10 of the Office Action. Pittman also fails to teach or suggest peptides having either of these specific sequences. Regarding the claimed sulfonated peptides, the Office admitted that Hortin also fails to teach such. Page 10 of the Office Action. Pittman, at best, only suggests that sulfonation affects the rate of activation by thrombin, and that sulfonation of factor V is required for rapid cleavage by thrombin.

It is respectfully submitted that in reaching the present conclusion of obviousness, the Office has unwittingly engaged in impermissible hindsight reconstruction. That is, without having the benefit of Applicant's claims which expressly identify the sequences DYDY and DYDYQ, the cited prior art would not lead a

practitioner in this field to arrive at the claimed subject matter. "Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'" Grain Processing Corp. v. American Maize-Products Corp., 840 F.2d 902, 5 USPQ2d 1788 (Fed. Cir. 1988). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). "Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." ATD Corp. v. Lydall, Inc., 159 F.3d 534, 48 USPQ2d 1321 (Fed. Cir. 1998).

And, as previously explained, the recent KSR decision by the Supreme Court and the Ortho-McNeil decision by the Federal Circuit, upheld the TSM test and its use to prevent improper hindsight reconstruction of claims using prior art. Therefore, in properly applying the TSM test to the present matter, there must exist some teaching, suggestion or motivation in the prior art to combine the references in the manner that the Examiner has done.

It was expressly admitted on page 10 of the Office Action that "Hortin does not teach...the tetrapeptide DYDY or the pentapeptide DYDYQ." Beginning with that premise then, where is any express teaching in the references to Pittman, Bakker, or Ramabhadran to combine them with Hortin? None of those references teach or describe the claimed peptides DYDY or DYDYQ. And so, how are either of these specific sequences obvious? In fact, the Bakker reference as previously explained

actually teaches away. For this reason alone, Bakker certainly provides no teaching, suggestion, or motivation for combining with any of the other references.

In the most recent Action, the Office argued that it was not engaging in hindsight reconstruction because "any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning." Page 13. In support of this, the Office cited In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

However, it must also be recognized that any type of hindsight reasoning can not be assisted with knowledge gleamed from an applicant's application, Ex Parte Takenaka et al., Appeal No. 2006-3046, Application No. 10/130,596, January 12, 2007 (Board citing application of In re McLaughlin with qualifications). As explained herein, the present rejection was only reached by benefit of the present application and disclosure of the specific amino acid sequences DYDY and DYDYQ. These sequences have been discovered to directly bind to thrombin and thus serve as anticoagulant agents. No teaching was identified in any of the cited art for these specific peptides. In point of fact, it was admitted by the Office that the primary reference, i.e. Hortin, does not teach these specific peptides.

It would be extremely unlikely, if not impossible, to arrive at the present invention from the four (4) cited references. As evidence of this, it is noted that all four references were available fifteen years ago. Yet, up until Applicant's discovery and present filing, the subject matter recited in the pending claims had not been previously disclosed! For at least these reasons, the present rejection must be withdrawn.

E. "Routine Experimentation" is Not the Standard

Apparently recognizing the "leap" made from the collection of prior art to the claimed subject matter, the Office fills in this extensive gap by asserting, "the selection of the peptide sequence and sulfation pattern would have constituted routine experimentation." In support of this, the Office cited KSR.[15] Pages 11-12 of the Office Action.

It is unclear why the Office now apparently asserts a new standard for obviousness rejections. By contending that the claimed subject matter was arrived at by "routine experimentation," the Office is apparently basing patentability upon the manner by which the invention was discovered. There is no such basis in the law for this. In point of fact, this is prohibited by statute: "Patentability shall not be negatived by the manner in which the invention was made." 35 USC §103(a).

It is acknowledged that the KSR decision now enables the Office and Examiners, when undertaking an obviousness analysis, to take account of the inferences and creative steps of a person having ordinary skill in the art, rather than having to identify precise teachings in the art directed to the specific subject matter of the claims. However, it is respectfully submitted that a fair reading of the cited references, **performed without the benefit of Applicant's disclosure,** would not lead one to arrive at the claimed subject matter.

[15] The Supreme Court in KSR referred to "routine experimentation" not as any type of standard by which to determine obviousness, but instead as only one of many factors that should be considered in an "articulated reasoning" approach.

Again, if the claimed subject matter could have been arrived at by mere routine experimentation, then why has Applicant's discovery never been disclosed prior to the present application?

The Graham factors still control an obviousness inquiry. No such analysis and application of those factors were undertaken in the rejection of the claims at issue. For at least this reason, the present rejection fails, and must as a matter of law, be withdrawn.

V. Conclusion

It is respectfully submitted that the present application is in a condition for allowance and notice to that effect is hereby requested. If it is determined that the application is not in a condition for allowance, the Examiner is invited to initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application.

If there are any additional fees resulting from this communication, please charge same to our Deposit Account No. 18-0160, our Order No. CSU-17999.

Respectfully submitted,

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